UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/929,772	08/14/2001	Robert T. Lum	96,877-W1	2293

7590 09/09/2002

A. Blair Hughes
McDonnell Boehnen Hulbert & Berghoff
32nd Floor
300 S. Wacker Drive
Chicago, IL 60606

EXAMINER	
BERCH, MARK L	
ART UNIT	PAPER NUMBER
1624	9

DATE MAILED: 09/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/929,772	LUM ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50-88 and 91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50-88, 91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The elimination of the substituted aryl option for R'1 establishes a line of demarcation with WO 97/16452, and so no art rejection is made over this reference.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 50-57, 60-61, 63-65, 67-71, 73-75, 79-83, 85, 87-88, 90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meijer.

See Table 1, species 4 and 9-16. The third proviso bars the situation where there is 6-benzylamino and 9-sopropyl, so these species are barred. However, the variant of these species with 9-methyl is obvious because such a choice appears in species 6. And the variants with 6-cyclohexylmethyl or isopentenylamino or 3-iodobenzylamino are also taught because these are species present in the table as well.

The traverse is unpersuasive. No hindsight is being employed. The reference explicitly teaches that R9 can be alkyl generally, thus pointing to the obviousness of any alkyl. Species 6 then provides the specific motivation or guidepost to the exact methyl choice. The same is true for the substituent at the 6-position. Indeed, the benzyl and isopentenyl choices are listed in the last line on column 3 as two of the three preferred choices, a clear teaching of equivalence, and an explicit motivation to use these interchangeably. And the cyclohexylmethyl choice is named 3 lines earlier.

Claims 50-57, 60-61, 63-65, 67-71, 73-75, 79-83, 85, 87-88, 90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schow.

The new proviso excludes the two species of the reference. However, the claims still embrace the position isomers of these two species. Thus, for species 9, while the proviso excludes the 2-amino ethyl substituent, the position isomer, the 1-amino ethyl, is still included. Likewise for compound 14, the amino methyl could be at the 1 position, or the amino could be at the 1 or the 2 position of the ethanol piece. It is well established that position isomers are prima facie structurally obvious even in the absence of a teaching to modify. The isomer is expected to be preparable by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing the position isomers. This circumstance has arisen many times. See: *Ex parte Englehardt,* 208 USPQ 343, 349; *In re Mehta,* 146 USPQ 284, 287; *In re Surrey,* 138 USPQ 67; *Ex Parte Ullyot,* 103 USPQ 185; *In re Norris,* 84 USPQ 459; *Ex Parte Naito,* 168 USPQ 437, 439; *Ex parte Allais,* 152 USPQ 66; *In re Wilder,* 166 USPQ 545, 548; *Ex parte Henkel,* 130 USPQ 474; *Ex parte Biel,* 124 USPQ 109; *In re Petrzilka,* 165 USPQ 327; *In re Crownse,* 150 USPQ 554; *In re Fouche,* 169 USPQ 431; *Ex parte Ruddy,* 121 USPQ 427; *In re Wiechert,* 152 USPQ 249, *In re Shetty,* 195 USPQ 753.

For example, "Position isomerism has been used as a tool to obtain new and useful drugs" (Englehardt) and "Position isomerism is a fact of close structural similarity" (Mehta, emphasis in the original). See also MPEP 2144.09, second paragraph.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 50-88, 90 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 48-74, 76 of copending Application No. 09/929771. Although the conflicting claims are not identical, they are not patentably distinct from each other because overlapping subject matter is involved here and in the sibling case. For example, claim 55 in 09/929771 specifies R4 as 2-amino ethyl, a choice depicted in claims 68 and 73 here.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 91 provides for the use of the claim 50 compounds as herbicide, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 91 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 50-67, 72, 77-88, 90-91 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The third proviso lacks description in the specification. The "and" in the third from last line of page 36 does not appear on page 78, line 7, after the first comma, nor

on page 12, line 9. There is no way of knowing whether "and" or "or" was intended missing word. For whichever choice is made, applicants must show that one of ordinary skill in the art would have known that this choice, and not the other, was intended.

The traverse is unpersuasive. Applicants insist that "to read the third proviso to contain any word other than "and" would be contrary to common sense" but applicants give no reason why "and" is any more correct than "or". Basically, the Boolean operator in front of "R2 is isopropyl" is missing. The choices of "and" and "or" are both plausible. That is, the choices of 1) "and R2 is isopropyl" and 2) "or R2 is isopropyl" both make perfect sense, and there is no way of knowing which was actually intended. In 1), the choices of benzylamino, etc are barred when both conditions are met, i.e. when R3 is not 2-hydroxyethylamino and R2 is isopropyl. In 2), the choices of benzylamino, etc are barred when either condition is met, i.e. when R3 is not 2-hydroxyethylamino or R2 is isopropyl.

Claims 50-55, 57, 60, 63-64, 68-71, 73-75, 77-88, 90-91 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The newly added proviso lacks description. Even a negative limitation requires description, *Ex Parte Grasselli,* 231 USPQ 393.

Claim 81 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Nowhere does the specification state this specific utility for the genus. Note for example that this covers not only diseases caused by abnormal cell proliferation, but diseases which cause abnormal cell proliferation.

Claims 81-85, 87, and 90 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The compounds are disclosed to be CDK2 inhibitors, and in some cases, inhibitors of IκB-α kinase. There is no reason to think that one of ordinary skill in the art could, without undue experimentation, treat such difficult disorders with such compounds. Note the following:

A. References of cited in the parent do not support such a notion. Glab(1994) does not mention therapeutic utility. Others present use only as a possibility to be achieved by developing much better compounds. For example, Vesely (1994) says, "It is possible that, through its specificity, olomoucine may lead to a compound which will preferentially inhibit the proliferation of certain tumor cells." Applicants urge that "the Vesely citation is taken out of context." The examiner does not agree; the quote speaks for itself, and does not appear any different when viewed with the sentence(s) which come before it or after it. Olomoucine is excluded by proviso from the claims. This shows that basic research is still required to obtain the necessary selectivity. Abraham (1995) says that "olomoucine may constitute a lead compound for the design of new

anti-tumor agents." Similarly, Schultz-Gahmen (1995) referring to its results, says it "should prove useful in modifying and improving the lead compound." But, a lead compound is one which is not actually ready for use; it is by its nature something which needs to be modified by additional research. The traverse on this is not agreed with. A compound does in fact have to be ready for use; it has to be the actual compound which is to be used, and not something which needs to be undergoing "modifying and improving." It is agreed that "It is not fatal if some experimentation is needed", but it still has to be the compound itself that is ready, not one which is merely something to be modified and improved to get it to work.

B. Although olomoucine itself is not potent enough to be effective, the testing presented in Table 7 established that many of these compounds are either less effective as CDK2 inhibitors than olomoucine, or are not effective to actually inhibit cell proliferation even in this crude test, or both. Indeed, a number of species displayed no measurable activity in either test. The specification says that cell proliferation inhibition has an IC(50) of "preferably less than 0.5 μg/ml" which is a reasonable standard, but only 4 species met that standard; the other 20 species tested did not. Even on this very simple *in vitro* test, the results show that most compounds are ineffective. Applicants reply, "Presumably the Examiner does not doubt that Applicants' compounds of the invention are CDK inhibitors. This is well established in Example 7 of the invention." The examiner does indeed doubt this. Many compounds were not tested, but of those that did, many had little or no demonstrated efficacy. Thus, in the first 7 on page 64, three of them have IC(50) values which are so high that they have no meaningful potency, and four had no demonstrated activity at all. Applicants also argue, with regard

to the fact that their compounds are generally less potent than olomoucine, that "potency is not the only measure of effectiveness of a drug." Applicants list then stability, etc. Potency is the best measure (but not only consideration), and moreover, there is no reason to think that their compounds are any more stable than olomoucine, or that olomoucine has any e.g. stability problem in the first place. Thus, in summary, applicants compounds are generally speaking less effective than a compound which has never been made to work, and nearly all the tested compounds failed applicants own standard of "preferably less than 0.5 μg/ml".

C. Claims 83 and 85 call for the treatment of cancer in general. However, there never has been a compound capable of treating cancer generally. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task. Applicants cite cisplatin, antimetabolites, etc which "have all been used to

treat more than one type of cancer." This is true, but none of these can be used to treat cancer generally, or anything even remotely close to that, which is what these claims call for. In fact, there are many, many kinds of cancer which do not appear to respond to chemotherapy at all. Just as an example, many forms of CNS cancers cannot be treated with chemotherapy. This is because 1) the blood-brain barrier, which is often intact in parts or all of a brain tumor, will block out many drugs, as it is the purpose of the blood-brain barrier to protect the brain from alien chemicals, and 2) CNS tumors are characterized by marked heterogeneity, which greatly decreases vulnerability to chemotherapy. As a result, many categories of CNS tumors simply have no chemotherapy available. These include, generally, hemangiomas and hemangioblastomas, low grade gliomas, meningiomas, craniopharyngiomas, acoustic neuromas, pituitary adenomas, optic nerve gliomas, glomus jugulare tumors and chordomas, to name just some. Further, this specification fails to actually name which cancer(s) these compounds would be expected to be effective against. Since there are no established anticancer agents structurally related to these compounds, this lack of disclosure places an improper burden on the public to figure out how to use the compounds. The sole testing done in this regard appears on page 50. At 3 dosage regimens, the tested species met the minimum standard of efficacy, T/C = 130. However, compound 3 is by far the most potent as noted below. In terms of the ability to inhibit cell proliferation, the next most potent compound tested had only 1/6 its potency and hence would not be expected to pass even this crude screening test with L1210. The evidence of record is thus that this compound is not representative of the genus as a whole; it is by far the most potent, in terms of CDK2.

D. Further, claim 81 is even broader, covering presumably any cell proliferative disorder. A proliferative disorder is anything that causes any abnormal tissue that grows by cellular proliferation more rapidly than normal, or continues to grow after the stimulus that initiated the new growth has ceased, or shows lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such a term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, and polyps. In addition, it embraces various non-cancerous proliferative disorders such as vascular smooth muscle proliferation associated with atherosclerosis, glomerular nephritis, clonal proliferative disorders including the various Myelodysplastic Syndromes such as Refractory anemias, certain types of abnormal wound healings, different types of abnormal angiogenisis, pulmonary fibrosis, macular degeneration, myeloproliferative disorders such as primary polycythemia and myleofibrosis, and rheumatoid arthritis. There is no such thing that an agent which is effective against such disorders generally, since they are so diverse, nor is there any reason to think that such an agent could be made to work. The traverse is unpersuasive. It essentially asserts that since these compounds inhibit CDK-2 and IκB-α, then they can inhibit all cell proliferation. However a) The Table 7 testing shows that many compounds did not inhibit CDK-2 at all, and still other had levels (e.g. 40 or 60 μg/ml; compare to olomoucine at 2.1) so high as to be considered inactive b) with regard to IκB-α, see point G below c) the notion that all cell proliferation disorders involve CDK-2 is completely mistaken. For example, the first step is the progression from G0 to G1, in which CDK-2 has no role. Further, the actual cell division itself takes place during M-phase. This has both Mitosis, the division of a cell's nucleus , including

the Prophase, Prometaphase, Metaphase, Anaphase, and Telophase processes, as well as cytokinesis, the division of the cytoplasm, which results when a fiber ring composed of actin around the center of the cell contracts, pinching the cell into two daughter cells, each with one nucleus. CDK-2 has nothing at all to do with this M-phase. Thus, if a disorder involved either of these steps, a CDK-2 inhibitor would be totally irrelevant.

E. The inclusion of gout in claim 83 makes no sense at all. Patients with gout are normally told to avoid high purine foods, in order to reduce uric acid secretion. The traverse is unpersuasive, and does not deal with the issue raised. Instead, the argument appears to be that these compounds will "reduce the number of proliferating clones of immunocytes", but there is no evidence whatsoever that this is true.

F. Systemic lupus erythematosus (SLE) is a complex disorder, an autoimmune disease characterized by immune dysregulation resulting in the production of antinuclear antibodies (ANA), generation of circulating immune complexes, and activation of the complement system. It is a difficult disorder which can be fatal. Applicants point out that treatments include methotrexate. Agreed, but so far as the examiner is aware, methotrexate is not a CDK-2 inhibitor. It is true that cell growth is involved in Lupus. However, cell growth is involved in the vast majority of diseases, so by this reasoning, applicants compounds would be effective for most diseases, period. Applicants have presented no nexus between SLE and CDK-2 inhibition. The same is true for MS. Multiple Sclerosis (MS) is a chronic disease of the central nervous system. Viral and autoimmune etiologies have been postulated. While genetic and environmental factors are known to contribute to MS, the skill level in this art is so low that a specific cause for this disease has not been not identified. Corticosteroids,

Interferonß-1B (Betaseron) as well as Interferonß-1a have been used with some limited success. However, so far as the examiner is aware, a) CDK-2 inhibitors have not been successfully employed against MS and b) immunosuppressive agents have not been convincingly established as effective against MS. A great deal of research has gone into the use of immunosuppressive agents for MS, but their use remains very controversial. However, applicants have not established that their compounds actually are immunosuppressive agents.

G. It is noted that this application discloses an additional property which "some of the compounds of this invention" (specification, page 3; emphasis added) have, viz, inhibition of IκB-α kinase. However, it is noted that a) it is unclear which compounds actually have this property, aside from the ones tested on page 75 and which were active, b) it is not clear which of the utilities in these rejected claims are connected to this property. Applicants in several places refer to these compounds being used to treat inflammatory disorders, including arguing specifically that it is effective against diseases such as rheumatoid arthritis which involved pro-inflammatory cytokines. In rebuttal, the examiner must point out that these compounds are alleged, in both the remarks and the specification, to be inhibitors of IκB-α, although the data shows them to be somewhat weak in that regard (and non-existent for a few species tested). However, if true, that would indicate that these compounds would make inflammation worse, not better. In this regard, the Carlet, ADVANCES IN SEPSIS Vol 1 No 3 2001, page 93 reference is cited. Figure 1 shows that Corticosteroid anti-inflammatory treatment starts by activation of IκB-α, which then inhibits NF-κB. That is, IκB-α is an inhibitor of NF-κB; that inhibition causes decreased transcription for proinflammatory cytokines, COX-2,

ICAM-1, VCAM-1 and increased transcription for IL-1ra. Thus, one wishes to activate IκB-α in order to get suppression of the proinflammatory cytokines, but these compounds are alleged to provide inhibition of IκB-α. Thus, any inflammatory disorder mediated by proinflammatory cytokines (which would include α-TNF, IL-1, IL-2, IL-4, IL-6, IL-8, IL-12, LT, IFN-α, INF-γ, and assorted chemokines), COX-2, ICAM-1, VCAM-1 would be made worse by this inhibition of IκB-α. This does not include all inflammatory disorders of course but does include many of them.

Claims 50-88, 91 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 50's proviso at third from last line of page 3 still needs to be modified, because its first condition is always met (i.e. R3 is never 2-hydroxyethylamino).
2. There are still some species in claim 76 which violate the first proviso. For example, the first species, the one that starts in the third line of claim 76 with a left brace does not have the substituent that the first proviso requires. Likewise the species that starts at the end of line 10, and there are others.
3. Claim 76 is garbled; the species which applicants seek to remove are still present, just enclosed in brackets. Note that the marked up text, and the clean text are the same.
4. The claims state "2, 6, 9 trisubstituted" but R_2 is permitted to be H, which gives just disubstituted. The traverse is unpersuasive. Things are not "substituted" by H. H being present mean that it is unsubstituted, not substituted. The preamble needs to state di-substituted or tri-substituted to be accurate.

5. The R_1' at page 4 line 2 should be R'_1.
6. There still remains original point 6. The text for R3 says, "hydrocarbons selected from the group consisting of ... acyl, heterocyclyl ... heteroaryl ... and heteroaralkyl." But these are not hydrocarbons. The same problem occurs for R2. The members of the set listed do not actually fall within the set; an e.g. acyl is not a hydrocarbon because it must have an oxygen present.
7. At page 4, line 2, that should be "4-methoxybenzyl"; the "amino" part needs to be removed as it is not part of that variable.
8. The variable R22 was removed from claim 50 as a choice for R'1, yet it appears in claims 51-53 and others, making these claims improperly dependent on claim 50
9. The deletion of "each" leaves the "having one to 20 carbons" (e.g. R3 definition) unclear. What is it describing? Is it the entire list preceding? In that case, the deletion of "each" made no difference, and original point 9 still remains. If it refers to just the preceding term, "alkynyl" then it makes no sense, since alkynyl cannot have just one carbon. Note what was correctly done at R^{22} definition.
10. Bracketed out material appears in the first line of the clean copy of claim 78.
11. The last phrase in claim 90 is unclear. Derived from how? It is noted that most solid tumors need additional blood supply for rapid growth, and they obtain this by rapid growth of new blood vessels, which is of course done using endothelial cells, so that the cancer can be said to be derived from such cells. Is that what the claim intends, i.e. solid tumors generally? Or do applicants intend just things like endothelioma? More precisely language is needed. Whatever choice is

selected must be supported by the specification. The traverse is confused. It refers to an amendment, but none was tendered.

12. "Amide" (e.g. page 4, line 8) is indefinite. There is no way of knowing whether applicants intend just carboxylic acid amides, or whether sulfonic, phosphonic, etc amides are intended. But even if carboxylic acid amido is intended, the term is undefined. Such a molecule generically has the formula RC(O)NR'R". One of the R choices will be used to attach, depending on whether the amido is C- or N-bound. What is the nature of the other two R groups? Can the two of them together form a ring, and if so, of what type? The term "aryl or aryl or heteroaryl" before the "amide" doesn't really answer the question. Do these terms define the R, the R', or the R" or is it any of them? And does that mean that all the substituents must come from that list, or just that it must be present? For example, if this were understood to be carboxamide bounded via the C, i.e. -C(O)NR'R", would C(O)N(alkyl)(alkenyl) qualify? It does have the alkyl, which is on the list, but it also has the alkenyl, which is not on the list. Moreover, it should be "amido" as this is a moiety. The traverse is unpersuasive. It simply does not address the issues involved.

13. A number of the claim 83 disorders are not considered a "cell proliferative disorder". a) Gout is a manifestation of hyperuricemia. Crystals of sodium urate cause acute inflammatory arthritis. It is not treated with antiproliferative agents. Symptoms are treated with anti-inflammatory agents. Gout itself is treated with **Colchicine , a microtubule inhibitor which appears to inhibit migration of white cells to affected joints and Allopurinol which is a competitive**

inhibitor of xanthine oxidase and thus causes excretion of hypoxanthine and xanthine instead of conversion to urate. The traverse here appears to completely misunderstand the meaning of "cell proliferative disorder." A cell proliferative disorder is anything that causes any abnormal cell growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. The remarks seem to indicate that applicants are using a vastly broader definition, in which "cell proliferative disorder" is any disorder in which the proliferation of cells is part of the body's response. It is correct that there is cell growth e.g. monocytes (the remarks refer to "immunoreactive T-cells, but that is believed to be mistaken; these are not involved in gout) in the body's response to the urate crystals. But that does not make it a "cell proliferative disorder" according to the normal understanding of the term. If applicants definition of the terms were to be used, nearly all diseases will qualify as a "cell proliferative disorder" , since nearly all involve some sort of cell growth. b) Multiple Sclerosis is of unknown cause, although it may be of immunological origin. It is not characterized by cell proliferation, but is a destruction of the preformed myelin. Treatment does not involve standard antiproliferative agents, but instead involves the use of corticosteroids, and even that is for symptom relief; it does not treat the underlying disorder. It is discussed above in point F. The same issue arises with the traverse here. c) Similarly, lupus (SLE is assumed) arise from hyperactivity of the immune system. d) "Host graft" is not a medical

term as set forth below in point 20, and so its inclusion is not proper. e) Type I diabetes is a disorder of the carbohydrate mechanism caused by little or no endogenous insulin. The traverse is not understood. The examiner did not actually say that it was an autoimmune. It is correct that lymphocytes destroy the beta-cells in the islets of Langerhans, whereas the lymphocytes should not do that. This does not mean that Type I diabetes is a "cell proliferative disorder". f) Rheumatoid arthritis is generally classified as an autoimmune disorder, but applicants seem to be assuming that any autoimmune disease by its very nature is a "cell proliferative disorder", which is simply not true.

14. The last 3 claim 78 choices are not permitted by claim 50, on which this ultimately depends, so the claim is improperly dependent on claim 50. Substituted aryls were deleted.

15. The choice of "thiomethoxy" seen in e.g. third from last line of page 20 is unclear. Is methylthio (CH_3S-) intended or is mercaptomethoxy ($HSCH_2O$-)? Something else? Whatever choice is selected must be supported by the specification. The traverse is unpersuasive. The drawing given makes no sense whatsoever. It isn't any kind of phenyl; the ring is a cyclohexabutadienyl ring. The S isn't a thio, but a thioxo

16. R_2 as cycloalkyl (e.g. claim 61) and substituted cycloalkyl (e.g. claim 72) makes the claims improperly dependent on claim 50, which does not provide for such choices. The definition in the specification cannot be relied on because it is defective. The traverse is unpersuasive. The standard meaning of alkyl does not permit a cycle. The Academic Press Dictionary of Science and Technology

reference, http://www.harcourt.com/dictionary/def/3/7/6/7/376700.html ; the Hawley's Condensed Chemical Dictionary, 13th edition (1977) page 34 reference; the Hackh's Chemical Dictionary, 3rd edition page 33 (1944) reference and the On-line Medical Dictionary http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=alkyl&action=Search+OMD all set forth alkyl in terms of - C_nH_{2n+1}, i.e. a non-cyclic group. Applicants need to list the cycloalkyl separately.

17. The last claim 60 term should have 20 as a superscript, not a subscript.

18. What in claim 79 is a "cationic salt" -- what is the cation? Is for example a N of the purine being quaternized? The traverse is unpersuasive. The term is not "defined" on page 24, lines 15-20; that merely gives some examples. The above does not happen to be one of the example types, so it is still unclear whether it is to be included.

19. The last 3 claim 78 choices are not permitted by claim 50, on which this ultimately depends, so the claim is improperly dependent on claim 50. Substituted aryls were deleted.

20. In claim 83, "host graft disease" is defective. The traverse is unpersuasive. Applicants state that "host-vs.-graft disease" is not intended, but that "host graft disease" is a "well known phenomenon". That is not true. The examiner has reviewed the three major medical dictionaries, Stedman's Medical Dictionary, On-Line Medical Dictionary, and Dorland's Illustrated Medical Dictionary and not found the term present at all.

21. Claim 57 provides R'_1 to be optionally substituted aryl, but that material was removed from claim 50, so that the claim is improperly dependent on claim 50.

22. Similarly, the first two species of claim 77 are substituted aryls, not permitted by claim 50.

23. There still remains original point 23. While it was fixed in claim 50, R^{22} is used as a substituent in other claims such as 51-53.

Specification

The parentage is still not correct. It says "... which is a section 371 application of ..." but in fact, it is a CIP of the PCT application.

This case lacks a proper abstract; the one provided is too brief as to structure of the compounds. Some definitions are needed for variables.

The scheme on page 28 is defective. The three steps must recite a reagent used, not a bare moiety. The same problem occurs on page 46. The traverse is unpersuasive. The scheme is simply not correct. Applicants are again urged to implement the changes which were made in 08/692012 as well, e.g. for the "serinol" on page 64, which is not a moiety at all, as many of the same errors are here as well.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 703-308-4718. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 308-4716. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 708-308-1235.

Mark L. Berch
Primary Examiner
Art Unit 1624

September 6, 2002